SHORT REPORTS

Serum prolactin in epilepsy and hysteria

Differentiating between hysteria presenting in an epileptiform manner and epilepsy can present diagnostic difficulties. Differentiation is important, however, since management of the two disorders differs. Electrochemical stimulation of the medial basal hypothalamus in animal models increases prolactin release.[1] Therefore if the abnormal electrical activity in epilepsy passes through the midbrain it should raise the serum prolactin concentration. This paper reports an investigation of this hypothesis.

Patients, methods, and results

Initial studies of neuroendocrine abnormalities after epileptic seizures showed that the optimal time for observing serum prolactin changes after a fit was 15-25 minutes. Blood was therefore taken from patients with epilepsy and from patients with a diagnosis of hysteria 20 minutes after a clinical fit. All the hysteria patients had presented initially with a diagnosis of epilepsy, and the pattern of their seizures resembled major tonic-clonic seizures. Hysteria was diagnosed on positive criteria as well as negative neurological signs. Serum prolactin concentrations were also measured in patients after non-dominant unilateral electric convulsion therapy (ECT) with standard anaesthetic procedures. The patients were divided into the following four groups: (1) those with generalised tonic-clonic seizures lasting more than 30 seconds with generalised interictal electroencephalographic (EEG) abnormalities; (2) those with hysteria (two had coexisting epilepsy and generalised EEG abnormalities); (3) those given unilateral ECT; and (4) those with "minor convulsions" with brief periods of altered consciousness and focal or generalised EEG abnormalities.

The results are shown in the table. After a generalised tonic-clonic seizure the serum prolactin concentration rose sharply compared with baseline levels. In all but one patient the concentration rose to 1000 μU/ml or more postictally. Such rises were not seen after hysterical seizures. In three hysteria patients the concentration was lower than the baseline level. Serum prolactin was raised in all patients after unilateral ECT. No clear pattern was seen in patients in group 4 but two, one with complex partial epilepsy, had postictal concentrations exceeding 1500 μU/ml.

Baseline serum prolactin concentrations (μU/ml) and concentrations 20 min after a fit in patients with generalised epilepsy and patients with hysteria, and in patients before and 20 min after unilateral ECT

Generalised epilepsy (n = 9)		Hysteria (n = 7)		Unilateral ECT (n = 11)	
Baseline	After fit	Baseline	After fit	Before	After
400	3400	140	480	395	2890
250	3000	460	360	280	2820
480	2100	425	345	320	2520
400	1800	350	300	290	2040
640	1400		261	380	1920
650	1200	160	240	230	1830
415	1120	220	222	360	1440
	1000			140	1000
240	680			355	790
				480	740
				169	315

Comment

These results suggest that the serum prolactin concentration rises after a generalised tonic-clonic seizure and is maximal 15-25 minutes after an attack. In all patients but one it was above 1000 μU/ml. Patients with a clinical diagnosis of hysteria, presenting as major epilepsy, had no such rises in serum prolactin after an attack. The serum prolactin concentration after a seizure may therefore be useful in differentiating hysteria from epilepsy. This study indicates that when the prolactin concentration is above 1000 μU/ml, in the absence of other causes such as a high baseline level or medication, the attack is epileptic rather than hysterical. Since similar rises occur after unilateral ECT with anaesthesia and a muscle relaxant they are unlikely to be due to either muscular activity or anoxia. Probably a rise in serum prolactin concentration will occur only when there is abnormal neurophysiological activity in the midbrain hypothalamic region. After minor seizures the serum prolactin levels were not always high, presumably because the spread of seizure activity differs depending on the characteristics of the discharge. Since serum prolactin was considerably raised after a fit in one patient with complex partial epilepsy prolactin concentration may be an indicator for detecting "limbic" partial seizures. Further studies of neuroendocrine changes after epileptic seizures and ECT are in progress and may lead to a better understanding of epileptic mechanisms, particularly of some of the behavioural and somatic consequences of recurrent abnormal electrical activity in the brain.

I thank Drs J P Laidlaw and J W Allen of the Chalfont Centre for their help in this research, and to Dr R T C Pratt for collecting blood samples from patients undergoing unilateral ECT. The samples were analysed in the Department of Chemical Pathology at the National Hospitals for Nervous Diseases, Queen Square.

[1] Clemens, J A, *et al*, *Experimental Brain Research*, 1971, **12**, 250.

(*Accepted 10 October 1978*)

The National Hospitals for Nervous Diseases, Maida Vale and Queen Square, London WC1N 3BG

MICHAEL R TRIMBLE, MRCP, MRCPSYCH, consultant physician in psychological medicine

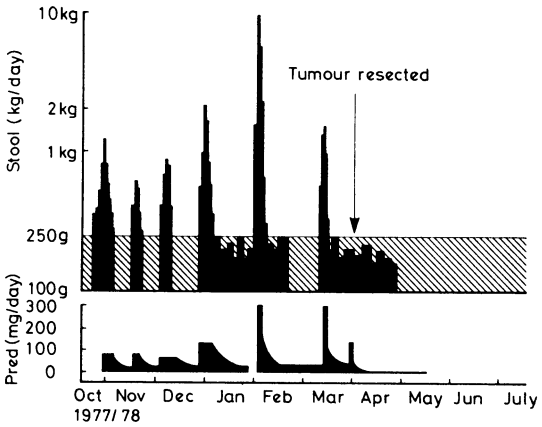
Vipoma: localisation by percutaneous transhepatic portal venous sampling

The watery diarrhoea syndrome of Verner and Morrison[1] is usually associated with a non-β islet cell tumour of the pancreas producing vasoactive intestinal peptide (VIP).[2] But tumours in sites other than the pancreas—particularly the adrenal medulla, sympathetic ganglia, and lung—may secrete VIP.[3] Cases of the watery diarrhoea syndrome have also been reported in which a tumour was present but did not secrete VIP or, indeed, in which there was neither tumour nor increased secretion of VIP.[4] When a pancreatic vipoma (tumour secreting vasoactive intestinal peptide) is present the syndrome is theoretically cured by removing the tumour, provided it has not metastasised. Diagnosis is often delayed, however, the average duration of symptoms before diagnosis being three years, and preoperative localisation of the tumour often difficult or impossible. We report here a case of watery diarrhoea syndrome produced by a vipoma which was localised by transhepatic venous sampling even though conventional diagnostic methods had failed to detect it. The syndrome was completely suppressible with corticosteroid—a feature of this disease often not appreciated. The interval between first symptoms and surgical cure was five months, the shortest recorded to our knowledge.

Case report

A 50-year-old man with no relevant history developed sudden, severe watery diarrhoea. On admission he was dehydrated, hypokalaemic, hypercalcaemic, and uraemic. He was treated empirically with intravenous fluid replacement and corticosteroids and rapidly recovered both clinically and biochemically (figure). Over the next four months he had several more attacks of watery diarrhoea, some very severe, which responded on each occasion to high doses of prednisolone. The figure shows their severity, episodicity, and response to corticosteroids. While in remission taking prednisolone 20 mg/day his serum biochemical values were normal. During an attack of severe diarrhoea investigations showed K^+ 1·9 mmol(mEq) l, urea 22·3 mmol/l (134 mg/100 ml), Ca^{++} 3·71 mmol(7·4 mEq)/l, plasma VIP 450 pmol/l (normal < 20 pmol/l). Other investigations were normal including serum gastrin, calcitonin, and parathormone concentrations; thyroid function tests; rectal and jejunal biopsy specimens; and barium meal, follow-through, and enema examinations.

A vipoma was considered the probable diagnosis, and localisation was attempted by conventional methods including coeliac, mesenteric, and hepatic arteriography; thyroid scan; intravenous pyelogram; and abdominal



Case of pancreatic vipoma. Daily stool weight (note logarithmic scale) and response to prednisolone from onset of symptoms to date.

and thoracic computerised tomography. These tests were all normal. Multiple systemic venous sampling via the inferior vena cava showed a moderately raised VIP concentration (80-150 mmol/l) in all veins draining into the venae cavae, but no peak was detected. The VIP concentrations in blood obtained by percutaneous transhepatic portal venous sampling were greatly raised all through the system, with a peak of >750 pmol/l at the junction of the splenic and superior mesenteric veins in the region of the head of the pancreas. In March 1978 a small tumour near but distinct from the head of the pancreas was removed. Multiple samples from portal vein radicals and systemic veins taken 10 minutes after resection showed that VIP concentrations had fallen to < 10 pmol/l. Histologically the tumour was a typical apudoma with immunoreactive staining for VIP. Five months later the patient was well taking no treatment with normal plasma VIP concentrations.

Comment

Several clinical aspects of the watery diarrhoea syndrome are exemplified by this case, in particular the associated hypercalcaemia, the corticosteroid responsiveness of the diarrhoea, and the difficulty in locating the tumour even when diagnosed. The site of VIP production was speculative until localised by portal venous sampling, thus allowing the surgeon to explore the region of the pancreatic head with confidence. This method of sampling has already proved valuable in localising pancreatic insulinomas both pre- and per-operatively.[5] We think that percutaneous transhepatic venous sampling is an accurate, safe, and quick method for tumour localisation in cases of vipoma when conventional diagnostic methods have failed.

We thank Dr A M Dawson, Mr M Birnstingl, and Dr Lesley Rees, of the Departments of Medicine, Surgery, and Chemical Pathology, for permission to report a case under their care and for helpful criticism.

[1] Verner, J V, and Morrison, A B, *American Journal of Medicine*, 1958, **25**, 374.
[2] Bloom, S R, Polak, J M, and Pearse, A G E, *Lancet*, 1973, **2**, 14.
[3] Said, S I, and Faloona, C R, *New England Journal of Medicine*, 1975, **293**, 155.
[4] Bloom, S R, in *Gut Hormones*, ed S R Bloom, p 583. Edinburgh, Churchill Livingstone, 1978.
[5] Turner, R C, *et al*, *Lancet*, 1976, **1**, 515.

(*Accepted 18 October 1978*)

Department of Gastroenterology, St Bartholomew's Hospital, London EC1A 7BE
J G C KINGHAM, MD, MRCP, senior registrar

Diagnostic Radiology Department, Royal Free Hospital, London
R DICK, FRCR, consultant

Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0HS
S R BLOOM, MB, FRCP, honorary consultant physician and senior lecturer in clinical endocrinology

Department of Endocrinology, Frimley Park Hospital, Frimley, Surrey
R J FRANKEL, MRCP, consultant

IgM platelet autoantibody due to sodium valproate

Thrombocytopenia and platelet dysfunction have been observed in association with sodium valproate treatment.[1] [2] One report[3] described findings compatible with an immune thrombocytopenia, but platelet antibodies were not found. Using a modified complement fixation test (CFT) consisting of serial dilutions of a standardised suspension of our patient's platelets to consume complement and prevent haemolysis of sensitised sheep erythrocytes, we were able to detect platelet-bound antibody. This technique is also semi-quantitative. Using the standard CFT[4] we were also able to detect an antiplatelet antibody in his serum at a time when the platelet-bound antibody was no longer detectable.

Case history

A 6-year-old mentally handicapped child was admitted to hospital on 2 May 1977 because of worsening epilepsy, which had been treated elsewhere. On admission he was hyperkinetic, and bruising was noted on the neck, right hand, and extensively on both legs. This was not accounted for by physical trauma. Sodium valproate (Epilim) 2000 mg daily, was his only medication. This dose was immediately reduced to 1000 mg daily. Phenytoin sodium, 100 mg twice a day, was introduced and 11 days later his clinical and haematological state had improved considerably.

Investigations showed: haemoglobin 11·4 g/dl; nucleated cells $3·7 \times 10^9$/l (differential counts, neutrophils $2·0 \times 10^9$/l, lymphocytes $1·4 \times 10^9$/l, monocytes $0·2 \times 10^9$/l, eosinophils $0·1 \times 10^9$/l); platelets 24×10^9/l. Blood film appearances confirmed thrombocytopenia. Platelet count 48 hours later was 27×10^9/l. Serum and red blood cell folate concentrations were normal. Bone marrow aspiration was postponed because of the frequency of his fits. Serum valproate concentration was 820 μmol/l (13·6 mg/100 ml) (recommended range 400-600 μmol/l (6·64-9·96 mg/100 ml)). Platelet-bound antibody was found and measured on two occasions using the modified CFT with patient's platelets. The results are given in the table. Nine months later,

Serological findings with concurrent sodium valproate doses and concentrations

Date	Dose of sodium valproate (mg/day)	Blood sodium valproate (μmol/l) (therapeutic range 400-600 μmol/l)	Whole blood platelet count ($\times 10^9$/l)	Platelet-bound autoantibody	Serum autoantibody test
May 1977	2000	820	24	+	NT
May 1977	1000	740	27	NT	NT
May 1977	1000	360	141	NT	NT
May 1977	1000	560	NT	NT	NT
May 1977	1000	NT	129	+ + +	NT
February 1978	1000	343	113	−	+ +
February 1978	1000	NT	142	−	+ +

NT = Not tested.
Conversion: SI to traditional units—Valproate: 1 μmol/l ≈ 0·0166 mg/100 ml.

during a social admission, he was reinvestigated. Serum antiplatelet antibodies were detected but platelet-bound antibody was not. The serum was subjected to gel filtration on a Sephadex G-200 column. Part of the serum was dialysed (1 ml; 2000 ml isotonic saline) to a valproate concentration of 31 μmol/l. Valproate assay of all fractions from the column was zero. A solution of valproate in normal saline was prepared and assayed at 1028 μmol/l (17·1 mg/100 ml). Dilutions down to 128 μmol/l (2·1 mg/100 ml) were prepared. The fractions (albumin, IgG, and IgM) were allowed to react with platelets from the patient and from normal subjects in the presence of each of the drug concentrations and in the absence of drugs.

Antibody activity was clearly detectable in whole serum and in the IgM fraction at all drug concentrations down to zero. The antibody titre did not vary with the drug concentration. Nine months after finding the platelet-bound antibody there was no activity in the IgG fraction. The IgM activity was eliminated by treatment with 2-mercaptoethanol. Bone-marrow aspiration showed increased numbers of megakaryocytes without platelet budding, despite the platelet count of 142×10^9/l.

Comment

An autoimmune response limited to an IgM antibody occurred in this patient. Antibodies investigated in idiopathic thrombocytopenic purpura have been IgG3 only.[5] Furthermore, the platelet count rose rapidly after halving the dose of sodium valproate. We believe, therefore, that sodium valproate was responsible and that in excess